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Source: Zhurnal Obshchey Khimii, Vol IX, No 5, 1939,
pp 406-408

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RESEARCH ON THE DERIVATIVES OF PYRROLE

I. SYNTHESIS OF CERTAIN N-ALKYL-SUBSTITUTED 2,5-DIMETHYLPYRROLE-3(4)-MONOCARBOXYLIC ETHERS

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(1) Synthesis of the 2,5-dimethyl-1-ethylpyrrole-3(4)-monocarboxylic Ether

Yu. V. Korshun obtained the substance in question from the interaction between α, β -diacetopropionic ether $\text{H}_3\text{C}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}(\text{COCH}_3)\cdot\text{COOC}_2\text{H}_5$ with ethylamine [1]. Yu. V. Korshun recommends to obtain diacetopropionic ether from nitroacetoacetic ether and monochloroacetone in ether solution [2]. Work with this method is not wholly without danger and does not give substantial advantages over the dangerless work with an alcoholic solution. True, Korshun points out that the alcoholic solution gives scantier yields of diacetopropionic ether, but this is explained by the fact that he carried the reaction through with heating. One should produce the reaction of nitroacetoacetic ether with monochloroacetone at room temperature. The following method of work gave me comparatively excellent yields of the pyrrole derivative. I dissolved 0.5 gram atoms (11.5 grams) of metallic sodium in 120 milliliters of absolute ethanol. After

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cooling, I introduced into the solution 0.5 gram molecules (65) grams of acetoacetic ether and then, still avoiding ⁱⁿ raise ~~the~~ temperature (cooling the flask with water according to need) I added 0.5 gram molecules (about 46.2 grams) of monochloracetone. Having left the reacting mixture to stand for 15-20 minutes at room temperature, I then introduced an alcoholic solution of ethylamine into the flask. Again having left the reacting mixture to stand for about a half an hour at room temperature, I then treated the product of the reaction with an excess of water. I thus obtained an oily sediment. I extracted this with ether. I dried the ether solution over calcium chloride and distilled the ether and subjected the residue to a fractionated distillation at the lowest possible pressure. I thus separated the pyrrole derivative containing chloracetone, acetoacetic ether and traces of acetopropionic ether in the way of impurities. During the fractionated distillation one should bear in mind that 2,5-dimethyl-1-ethylpyrrolmonocarboxylic ether resinificates with great ease with a temperature ^{more nearly} raise even at low pressures. Therefore the yield of the product is ~~higher~~ ^{more nearly} inversely proportionate to the temperature at which the fractionate distillation is conducted. Thus the yield of a first distillation at 40 millimeters, equaled approximately 6 percent of theory, while at 15-10 millimeters and especially at 5-2 millimeters, the yield approaches 9 and even 15 percent.

One also should bear in mind that it is necessary to subject the substance to distillation on the very same day on which it was synthesized -- this to avoid resinification.

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The pure 2,5-dimethyl-1-ethylpyrrolmonocarboxylic ether, just like the other N-alkyl-2,5-dimethylpyrrolmonocarboxylic ethers which I obtained, is rather stable. In order to purify the 2,5-dimethyl-1-ethylpyrrolmonocarboxylic ether which I had obtained from the above mentioned impurities, I processed it with 10-15 percent solution of caustic soda, then dried it and again subjected it to fractionated distillation at low pressure. Taking the fraction which boils at narrow range, I obtained a substance whose refractive index did not change during subsequent processing with alkali solution and further fractioning. Korshun described 2,5-dimethyl-1-ethylpyrrolmonocarboxylic ether as an oily liquid of yellowish color. The substance which I prepared changed even at room temperature into a crystalline mass saturated with an oily, viscous liquid. The crystals, once freed from that liquid, melted at 25-26 degrees and were white. The boiling temperature of the optically pure substance is 133-134 degrees at 2 millimeters. In its freshly distilled state it appears as an almost colorless liquid.

During the synthesis of N-alkyl-2,5-dimethylpyrrolmonocarboxylic ethers it was desirable to use as small a quantity of amines as possible. In calculating the indispensable amount of amine I started from the proposition that (1) the pyrrole derivative forms only at the expense of the reaction of amine with diacetopropionic ether as with an intermediate product of the reaction, (2) the yield of diacetopropionic ether under the conditions of work to which I adhered is equal to 30 percent. Correspondingly, at first I introduced into the reaction about 30 percent of the calculated amount of ethylamine.

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Experience has shown that the yield of the pyrrole derivative is better if one uses a certain excess of amine.

(2) Synthesis of the 1,2,5-trimethylpyrrole-3(4)-monocarboxylic

Ether

1,2,5-trimethylpyrrolmonocarboxylic ether was first obtained by Yu. V. Korshun. Then it was obtained by H. Fisher and K. Smeykal [4].

In this synthesis I utilized the method which gave me good results in the synthesis of 2,5-dimethyl-1-ethylpyrrolmonocarboxylic ether. In this case, during the first distillation I gathered two fractions: the first of these fractions boiled between 43 and 110 degrees, while the other boiled from 110 to 150 degrees at 5-6 millimeters. The second fraction practically contained the whole quantity of the pyrrole derivative formed. Already during the distillation of the second fraction, isolated crystals appear in the collector. During the first minutes the second fraction appeared as an oily liquid with a few scattered crystals. With time the second fraction changed into a crystalline mass saturated with a viscous oily liquid. After freeing it from the latter I processed the crystals with 10 percent caustic soda and then, after drying, I distilled them under lowered pressure. The crystals were white, a melting point of 48 degrees in agreement with literature data, a boiling point of 128-129 degrees at 2 millimeters. The yield of optically pure substance was about 15 percent of ~~theoretical~~ Theoretical value.

(3) Synthesis of the 2,5-dimethyl-1-propylpyrrole-3(4)-monocarboxylic ether

The 2,5-dimethyl-1-propylpyrrolmonocarboxylic ether was obtained by me by the same method I used to obtain the 1,2,5-trimethyl and the 2,5-dimethyl-1-ethylpyrrolcarboxylic ethers. As initial materials I used 65 grams of acetoacetic ether (0.5 gram molecule), 46 grams of monochloroacetone (about 0.5 gram molecule) and 10 grams of propylamine.

The pure substance melts at 44.5 degrees and boils at 144 degrees at 4 millimeters pressure. The yield is about 13 percent of theory. The quantitative measurements of nitrogen gave the following results:

0.2052 grams of substance: 12.1 milliliters N₂

(21 degrees, 742 millimeters)

0.2500 grams of substance: 15.2 milliliters N₂

(18 degrees, 745 millimeters)

Found %: N 6.69; 6.99

C₁₂H₁₉O₂N. Calculated %: N 6.69.

(4) Synthesis of the 2,5-dimethyl-1-butylpyrrolmonocarboxylic ether

Yu. V. Korshun held this substance in his hands but did not separate it in its pure state [5]. He simply obtained the corresponding acid in the analytical condition by way of saponification. Korshun

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obtained 2,5-dimethyl-1-butylpyrrolmonocarboxylic ether, processing diacetopropionic ether with butylamine. I obtained this substance by the method described above.

The optically pure substance which I obtained was in the form of an oily liquid of yellowish color. Crystals begin to separate during cooling of thin layers of this liquid in a cooling mixture. The temperature of their melting is so low that I was unable to isolate them at 15-16 degrees. The optically pure substance boils at 162-163 degrees under a 4 millimeter pressure.

The quantitative measurements of nitrogen gave the following results:

0.1600 grams of substance: 9.05 milliliters N_2

(17 degrees, 751 millimeters)

1.1761 grams of substance: 9.5 milliliters N_2

(18 degrees, 751 millimeters)

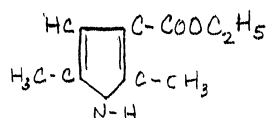
Found %: N 6.58; 6.25.

$C_{13}H_{21}O_2N$. Calculated %: N 6.27.

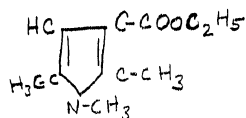
Not only a repeated fractionation at the lowest possible pressure, but also processing with alkali is necessary to obtain an optically pure substance. For this processing I applied 10 percent and even 15 percent alkali and observed no saponification at low temperatures.

The comparison of the melting points of those pyrrolmonocarboxylic ethers which I encountered during my work presents some interest.

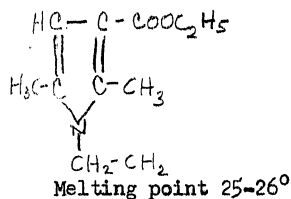
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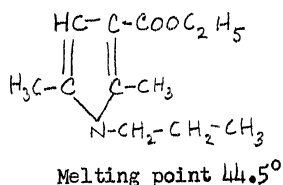
Melting point 117°



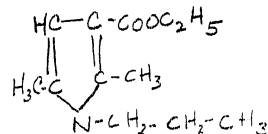
Melting point 48°



Melting point 25-26°



Melting point 44.5°



Harder to crystallize than the ethyl derivative

1-methyl group omitted

CONCLUSIONS

(1) Because of the scarce availability of alkylamines the method which I offer of obtaining N-alkyl-2,5-dimethylpyrrolmonocarboxylic ethers should be considered as practical.

(2) If the hydrogen atom of the NH-group which is present in the molecule of 2,5-dimethylpyrrolmonocarboxylic ether, is substituted by alkyls such as methyl, ethyl, n.-propyl, n.-butyl, there occurs a lowering of the melting point.

(3) The alkyl with an even number of carbon atoms lowers the melting point more than the preceding alkyl with an uneven number of carbon atoms.

(4) Butyl lowers the melting point more than ethyl.

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LITERATURE

- (1) Methods of Obtaining Pyrrole and its Derivatives, pp. 249, 250. Dissertation. Kharkov, 1907.
- (2) Cited Dissertation, p. 234.
- (3) Cited Dissertation, p. 2444.
- (4) H. Fischer and K. Smeykal. Ber., 56, 2374 (1923).
- (5) Cited Dissertation, pp. 253, 254.

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